Haploinsufficiency of BAZ1B contributes to Williams syndrome through transcriptional dysregulation of neurodevelopmental pathways.

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Public Summary:
Williams syndrome (WS) is a neurodevelopmental disorder that results in a cognitive and behavioral abnormality characterized by intellectual impairment, but also with relative strength in expressive language and hypersocial behavior. We used induced pluripotent stem cells to elucidate the molecular circuitry underpinning of WS. In patient-derived stem cells and neurons, we determined the expression profile of the critical deleted genes and the genome-wide transcriptional profile. Derived neurons displayed disease-relevant hallmarks and indicated novel aberrant pathways in WS neurons including over-activated Wnt signaling accompanying an incomplete neurogenic commitment. We show that haploinsufficiency of the ATP-dependent chromatin remodeler, BAZ1B, which is deleted in WS, significantly contributes to this differentiation defect. Altogether, these results reveal a pivotal role for BAZ1B in neurodevelopment and implicate its haploinsufficiency as a likely contributor to the neurological changes in WS.

Scientific Abstract:
Williams syndrome (WS) is a neurodevelopmental disorder caused by a genomic deletion of approximately 28 genes that results in a cognitive and behavioral profile marked by overall intellectual impairment with relative strength in expressive language and hypersocial behavior. Advancements in protocols for neuron differentiation from induced pluripotent stem cells allowed us to elucidate the molecular circuitry underpinning the ontogeny of WS. In patient-derived stem cells and neurons, we determined the expression profile of the Williams-Beuren syndrome critical region-deleted genes and the genome-wide transcriptional consequences of the hemizygous genomic microdeletion at chromosome 7q11.23. Derived neurons displayed disease-relevant hallmarks and indicated novel aberrant pathways in WS neurons including over-activated Wnt signaling accompanying an incomplete neurogenic commitment. We show that haploinsufficiency of the ATP-dependent chromatin remodeler, BAZ1B, which is deleted in WS, significantly contributes to this differentiation defect. Chromatin-immunoprecipitation (ChIP-seq) revealed BAZ1B target gene functions are enriched for neurogenesis, neuron differentiation and disease-relevant phenotypes. BAZ1B haploinsufficiency caused widespread gene expression changes in neural progenitor cells, and together with BAZ1B ChIP-seq target genes, explained 42% of the transcriptional dysregulation in WS neurons. BAZ1B contributes to regulating the balance between neural precursor self-renewal and differentiation and the differentiation defect caused by BAZ1B haploinsufficiency can be rescued by mitigating over-active Wnt signaling in neural stem cells. Altogether, these results reveal a pivotal role for BAZ1B in neurodevelopment and implicate its haploinsufficiency as a likely contributor to the neurological phenotypes in WS.